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How Toxic is Tritium? Relevance of High-Dose Results and Gamma-Ray Data to Evaluating Low-Level, Chronic Exposure

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Interest in tritium toxicity stems from concern not only with ^3H from small sources—its widespread use in research, for example, and in luminous paints (there have already been deaths from tritium exposure in the luminous paint industry)—but from the large source: nuclear energy. Tritium is a prominent by-product of nuclear fission, difficult and costly to contain, and impressive quantities find their way to the environment. When the fusion reaction becomes successfully harnessed for peaceful purposes, tritium will become even more important, because it is a fuel for nuclear fusion. Tritium will be increasingly with us in the foreseeable future, and it is essential that we possess a detailed understanding of its possible biological impact.

As an isotope of hydrogen (the cell's most ubiquitous atom), tritium can be incorporated into essentially all portions of the living machinery. Its preferred chemical state is water, ^3HOH, and as such it has free access to the body and to all living organisms. The main health and environmental concern is the possibility that significant biological effects may result from chronic exposure to very low concentrations of ^3HOH. But there is a serious lack of data for such exposure; current understanding of protracted irradiation at low levels is based primarily on information obtained with γ-rays. Therefore extrapolations are necessary for tritium, extrapolations from higher-level tritium doses, on the one hand, and from low-level γ-ray data, on the other. However, relationships between high- and low-level tritium exposures have not been adequately studied, nor between short- and long-term exposures; and with regard to γ-radiation, controversy exists over tritium's relative biological effectiveness (RBE), the necessary basis for extrapolation. The RBE has been variously reported, mostly between 1 and 2.5 for mammalian systems. There is lack of agreement too concerning the quality factor Q, related to RBE and used for radiation protection purposes. Recently Q was adjusted downward from 1.7 to 1, although it has been argued that a value of 2 would be more appropriate. This whole subject is in need of experimental reexamination. Firmer bases for extrapolation and hazard evaluation are required.

Experimental

We approached this problem by measuring effects of protracted, low-level ^3HOH exposure and γ-irradiation in the intact, developing mouse, using quantitative cell enumeration to determine the damage done to a particular cell population. The period of development was chosen since it is the most vulnerable portion of the mammalian life cycle, and oocytes were selected for study since they can be counted in the ovary, are highly radiosensitive, and are cells that can not be replaced after birth.

To obtain dose–response data for tritium, ^3HOH was administered in drinking water to mother mice throughout pregnancy and lactation, and effects were studied in their young. Body-water tritium levels were measured by radioassay of urine sam-

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ples, and numbers of primary oocytes surviving in the continuously exposed offspring were determined at 14 days after birth by microscopic counting in serial sections of ovaries and compared with controls. For the exposure range studied, 0.08–11 μCi/ml in body water, oocyte survival was found to decrease exponentially with dose. There was no threshold, and the LD_{50} level was 2 μCi/ml, which delivers a radiation dose of 0.44 rad/day. The effectiveness of tritium was constant over the more than 100-fold range of doses (and dose rates). Significant cell killing was measured at tritium levels low enough to be compared with maximum permissible concentrations for occupational exposure.

Since effects were found at such low levels of ^{3}HOH, it was all the more important to ascertain whether responses to a more "standard" radiation would be significantly different. Comparative studies were therefore carried out by using ^{60}Co γ-rays. Mice were exposed continuously from conception to 14 days after birth, as for ^{3}HOH, and surviving oocytes were enumerated in ovaries and compared with controls. The dose–response curve was less steep than for ^{3}HOH, with LD_{50} about 1 rad/day. In further contrast, the γ-ray curve was not exponential, but upwardly convex, indicating that the effectiveness of γ-radiation increased at higher doses (and dose rates). This agrees with expectations from the theory of dual radiation action for acute exposure or incomplete recovery, and, while unexpected with chronic exposure, indicates that recovery in these cells was not complete even though exposure was protracted.

From the dose–response curves for ^{3}HOH and γ-rays, the RBE could be evaluated. (The RBE is the ratio of doses from the two radiations that produce equal effects.) It was distinctly greater than unity, and, owing to the curvilinearity of the response for γ-rays, it varied inversely with dose. At 50 rads (of γ-rays) the RBE was 1.6; at 25 rads, 1.9. It continued to rise at lower exposures, reaching a value of 2.8. This is higher than other values reported; but it was determined here at low-level exposure, and is in close agreement with the low-dose RBE predicted on the basis of the theory of dual radiation action and physical microdosimetric measurements on tritium β particles and γ-rays.

^{3}HOH and γ-rays were also compared for shorter exposures (only 5 days duration). Dose rates were 4.1 and 5.9 rad/day, respectively, and mice were exposed from day 20 after birth to day 25. The RBE was found to be 1.4, lower than 1.9 observed at the same γ-ray dose with protracted exposure. Oocyte survival was higher for both radiations in the 25-day-old mice, however, owing to decreased radiosensitivity in the older animals. Therefore, doses for all experiments were normalized to allow unified comparisons. Normalization was based on data for oocyte radiosensitivity at various ages. The short-exposure RBE of 1.4 is then compared with 2.1 for protracted exposure, and the disparity increases. While differences in subcellular microdistribution of ^{3}H atoms (from differing times available for incorporation) may play some role, the normalized ^{3}HOH point falls on the line with chronic tritium data, suggesting that the RBE disparity is due mostly to a γ-ray dose-rate effect. Whatever the mechanism, it is clear that the RBE is higher for low-level, protracted exposure (where the need for evaluation exists) than for short, higher ones (where data are more easily obtained).

Conclusions

The experimental results considered here are for low-level, protracted ^{3}HOH and γ-ray exposures, and for higher-level, shorter-term (5-day) exposures. They were obtained by using an extremely radiosensitive, *in vivo,* mammalian system, and are in agreement with predictions from theory and physical microdosimetric measurements. With regard to extrapolations, they suggest the following general conclusions.

For evaluating protracted exposures to tritiated water, extrapolations can probably safely be made from higher-dose results. This follows because of the simple exponential character of the dose-response relation, indicating that effectiveness of tritium β radiation does not change appreciably with dose or dose rate (in the ranges studied here). The response curve may, however, bend gently downward at doses higher than we have examined. Such curvature might be expected from the theory of dual radiation action, and would introduce into extrapolations over- rather than under-estimation of effects at low exposure; hence extrapolations would remain on the safe side.

It is also probably safe to extrapolate from short-exposure ^{3}HOH results to chronic exposure, although caution is indicated; the possibility has not been excluded that a significant degree of especially effective subcellular microdistribution of ^{3}H atoms may occur with protraction of exposure.

It is not safe, however, to extrapolate from results for low-level γ-ray exposures (the major source of existing information on low-level, chronic irradiation) to low-level ^{3}HOH exposure unless an appropriate RBE factor (about 2.8) is used. Decreased effectiveness of γ-radiation at low doses re-

sults in tritium's being almost three times as damaging to living systems as are γ-rays at low-level exposure.

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